

## 2. RELEVANCE TO PUBLIC HEALTH

### 2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO TIN AND TIN COMPOUNDS IN THE UNITED STATES

Tin is a naturally occurring element. It is a silver-white metal that is malleable and somewhat ductile. The earth's crust contains about 2–3 ppm tin, comprising 0.0006% of the earth's crust. The most important tin containing mineral is cassiterite,  $\text{SnO}_2$ . U.S. consumption of primary (derived from ore) and secondary (recovered from scrap or waste) tin was 34,200 and 6,990 metric tons, respectively, in 2001 and is estimated as 37,000 and 9,000 metric tons, respectively, for 2002. The major uses of tin in 2002 were: cans and containers, 27%; electrical, 23%; construction, 10%; transportation, 10%; and others, 30%. Tinplate is used in food packaging, in aerosol containers, and for decorative applications. Various tin alloys are important, including bronze and pewter. The largest application of dibutyltin compounds are as polyvinyl chloride (PVC) stabilizers. Triorganotin compounds are used as industrial biocides, agricultural chemicals, wood preservatives, and marine antifouling agents.

Tin may be released to the environment from natural and anthropogenic sources. Tin is a component of many soils and tin and inorganic tin compounds may be released in dusts from wind storms, roads, and agricultural activities. In general, organotin compounds are released to the environment from anthropogenic sources. Methyltins may occur naturally, since they may be produced in the environment by biomethylation of inorganic tin by bacteria. Releases of tin to environmental media may occur from the production and use of tin and tin compounds. Organotin compounds, such as tributyltin and triphenyltin, enter the environment directly from their use as antifouling paints and as pesticides. To a lesser extent, organotin compounds may also enter the environment by leaching from consumer products and from the disposal of products containing organotin compounds in landfills. Cations of tin,  $\text{Sn}^{2+}$ , and  $\text{Sn}^{4+}$ , will generally be adsorbed by soils to some extent, which reduces their mobility. Tin is generally regarded as being relatively immobile in the environment. Many organotin compounds occur in water as cations, and would be expected to partition to soils and sediments.

Occupational exposure to tin may be significant in some industrial environments. Ambient environmental levels of tin are generally quite low, except in the vicinity of pollution sources. Human exposure to tin may occur by inhalation, ingestion, or dermal absorption. Dermal absorption is a significant route of occupational exposure for certain organotin compounds. However, exposure to tin is primarily by ingestion of food, especially canned food products. Tin-lined cans used to package food are the most important contributor to dietary tin intake. The average daily tin intake of an adult in the United

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States was estimated at 4.003 mg (4 mg from food and 0.003 mg from air), and with undetectable levels contributed by drinking water. An estimate of the daily tin intake in an adult in France, showed that canned foods, while representing 6–7% of the daily consumed foods, represented >95% of the total tin intake. The estimated tin intake from food was determined to be 0.04 mg/kg body weight. In a 1994 total diet study in the United Kingdom, the canned vegetable group and fruit product group contributed 66 and 31%, respectively, to the total average exposure of tin from food, which was estimated as 2.4 mg/day. From this study, an upper range exposure to tin of 7.9 mg/day was estimated. Population dietary exposure to tin from total diet studies in the United Kingdom from 1976 to 1994 ranged from 1.7 mg/day in 1985 to 5.4 mg/day in 1991. In a 7-day duplicate diet study of 97 pre-school aged (1.75–2.2 years) children from the Birmingham area in the United Kingdom, the average daily intake of tin was 1.78 mg/kg. In this study, mothers were asked to collect and weigh duplicate samples of all food and drink (including water) consumed by their children in and outside of the home. There was a significant correlation between the amount of canned food consumed and the concentration of tin in the diet. People eating a high percentage of their diet from canned foods will be exposed to higher amounts of tin than people eating more fresh foods. For example, people who live in institutional settings, such as nursing homes, boarding schools, or prisons, or people with lower incomes, may be served or choose canned foods due to their ease of storage and economical price.

Tin concentrations in foods will depend on whether they are packaged in lacquer tin-lined cans or unlacquered cans. Mean tin concentrations ranging from <1 to 1,000 mg/kg have been found in foods packaged in unlacquered or partially lacquered cans, while the average tin concentration in foods in lacquered cans has been reported to be 0–6.9 mg/kg. Data from the Can Manufacturers Institute indicate that >90% of tin-lined cans used for food today are lacquered. Only light colored fruit and fruit juices are packed in unlacquered cans, since tin helps maintain the color of the product.

Potential exposure for the general population to organotin compounds would be expected to exist for butyltin compounds, phenyltin compounds, and di- and monomethyltin, according to available monitoring data. The daily intakes of tributyltin and triphenyltin in Japan were estimated to be 0.0047 and 0.0007 mg in 1991 and 0.0022 and 0.0007 mg in 1992, respectively, based on a duplicate portion study. In this study, cooked meals were collected for 3 days from women in Shiga Prefecture, Japan in 1991 and 1992, and were homogenized and frozen. In a separate market basket study in Shiga Prefecture, Japan, daily intakes of tributyltin and triphenyltin in Japan were estimated to be 0.0069 and 0.0054 mg in 1991 and 0.0067 and 0.0013 mg in 1992, respectively. Of the food groups analyzed in the market basket study, 95% of the daily intakes of tributyltin and triphenyltin came from the fish, mollusks, and crustaceans food group. Household commodities made up of polyurethane, plastic polymers, and silicons contain butyltin

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concentrations in the parts per million (ppm) range. Butyltin compounds are also found in seafood from coastal areas. Mono- and dimethyltin and mono- and dibutyltin compounds have been detected in drinking water in Canada where PVC pipes, containing these organotin compounds, are used in the distribution of drinking water. It has been demonstrated that butyltin compounds in siliconized baking parchment can be transferred to food baked on this type of baking parchment. Organotin compounds were found in household dust in a United Kingdom study. Monitoring data were not found to indicate whether the general population is exposed to other organotin compounds, such as trimethyltin and triethyltin.

**2.2 SUMMARY OF HEALTH EFFECTS**

Numerous studies have been conducted on the effects of tin and related compounds in a variety of animal species (primarily rodents), but the data in humans are limited. The toxicity of tin and related compounds in animals has been investigated mostly following ingestion by the oral route. Most of the information on the health effects of inorganic and organic tin in humans comes from studies of individuals exposed at work, volunteers, and accidental or intentional exposures. Occupational exposures to tin involve mainly inhalation and dermal exposure. Descriptions of additional cases including, an accidental oral intoxication in France in 1954 of nearly 1,000 people with an organotin compound, can be found in WHO (1980). Several reviews of the health effects and environmental fate of inorganic and organic tin compounds have been published.

Humans chronically exposed to inorganic tin (e.g., stannic oxide dust or fumes) manifest a benign form of pneumoconiosis known as stannosis, which involves mainly the lower respiratory system. Gastrointestinal effects such as nausea, vomiting, and diarrhea have been reported in subjects ingesting food items contaminated with inorganic tin. There is no evidence that inorganic tin affects reproduction or development in humans or that it is a neurotoxicant, immunotoxicant, mutagenic, or carcinogenic agent in humans. A relatively limited number of studies in animals have not clearly established potential target organs for inorganic tin toxicity. Of the effects described, hematological signs of anemia and gastrointestinal distension appear to be best identified as tin-related. Other findings, such as liver degeneration and vacuolar changes in the kidneys, have been reported in some long-term oral studies, but not in others; at least not conclusively. Tin affects the metabolism of other metals such as copper, zinc, and iron; therefore, if the levels of these metals are not optimally regulated, it is difficult to ascertain whether a specific effect is caused by exposure to tin itself or is due to fluctuations in tissue levels of other metals. Bioassays for carcinogenicity of inorganic tin have been negative.

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Cases of lethality have been reported after acute inhalation exposure to a mixture of vapors of trimethyltin and dimethyltin organotins and after acute oral ingestion of trimethyltin. In addition, approximately 100 deaths occurred in France in 1954 following ingestion of a proprietary drug used to treat osteomyelitis, anthrax, and acne that seemed to have been contaminated with ethyltin triiodide, triethyltin iodide, or tetraethyltin. Those affected showed neurological signs and symptoms such as headache, photophobia, altered consciousness, and convulsions. These appeared about 4 days after intoxication and, in individuals who recovered, continuous headaches and weakness persisted for at least 4 years. Additional cases of accidental or intentional acute inhalation, oral, or dermal intoxication with trimethyltin or triphenyltin also have included adverse neurological effects that persisted for a long time (years in some cases) after the poisoning episode. Organotins also are known to be skin and eye irritants in humans.

There is no evidence that organotin compounds cause developmental or reproductive alterations in humans or that they cause cancer. Only one study was located that reported chromosomal alterations in human lymphocytes exposed to trimethyltin *in vitro*. Limited inhalation data from intermediate-duration studies in animals indicate that organotins can produce lung alterations, irritation of the respiratory airways, skin, and eyes, and liver and kidney effects. In contrast to the limited inhalation database, an extensive oral database indicates that trimethyltin and triethyltin compounds are primarily neurotoxic; whereas, tributyltin, dibutyltin, and dioctyltin are essentially immunotoxic. Hepatic and hematological effects also have been described in animals treated orally with organotins. Triphenyltin, dibutyltin, and tributyltin, when administered during pregnancy, have induced developmental and reproductive effects in rodents. However, it remains unclear whether these effects occur only at doses that induce maternal toxicity. Studies of genotoxic activity of organotin compounds have given mixed results depending on the specific compound and test system. Dibutyltin acetate, triphenyltin hydroxide, and tributyltin oxide have been tested for carcinogenicity in long-term bioassays. The first two compounds produced no evidence of carcinogenicity in Fischer-344 rats and B6C3F<sub>1</sub> mice, whereas the results for tributyltin oxide in Wistar rats were considered questionable by the EPA and led to a carcinogenic classification of “not classifiable as to human carcinogenicity” or, to a group of substances for which there is “inadequate information to assess carcinogenic potential,” according to updated guidelines. Additional studies with higher doses of triphenyltin hydroxide in Wistar rats and NMRI mice showed increased incidence of pituitary cancer in female rats and of liver cancer in female mice.

**Immunological Effects.** There is no evidence that tin or organotin compounds, at the concentrations found in the environment, alter immunocompetence in humans. However, tributyltins and other organotins have caused transient immune alterations in rats. The effect is characterized by reduced

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thymus weight and size and lymphocyte depletion. Dialkyltins appear to directly interfere with proliferation of thymocytes, a cytostatic effect, whereas tributyltin oxide has a direct and selective toxic action on lymphocytes in the thymus. A study in rats, which reported a depressed humoral response against immunization with sheep red blood cells (SRBC) following 4–6 weeks of exposure to dibutyltin dichloride, was used to derive an intermediate-duration oral MRL for this chemical. Long-term studies with tributyltin oxide in rats have demonstrated alterations in parameters of specific and nonspecific resistance at the relatively low dose level of 0.25 mg/kg/day. This study was used to derive an intermediate- and chronic-duration oral Minimal Risk Level (MRL) for tributyltin oxide. Although no adverse immunological effects have been described in humans exposed to tin and compounds, the high sensitivity exhibited by the rat thymus and the impairment in resistance to infection suggest that similar responses might occur in humans exposed to these chemicals at high concentrations or for long periods of time, should it be established that the rat is a relevant model.

**Neurological Effects.** While adverse neurological effects have been described in animals following oral exposure to various organotin compounds, triethyltins and trimethyltins are by far the most potent neurotoxins and have been the most extensively studied in experimental animals. The results from animal studies have confirmed the findings reported in cases of accidental or intentional exposure to trimethyltin and triethyltin in humans. Triethyltin produces brain and spinal cord swelling, which is characterized by accumulation of fluid between myelin layers, splitting of the myelin sheets, and formation of intramyelin vacuoles. This was observed in fatal cases that occurred from a massive accidental intoxication episode in France in 1954 and similar results have been reproduced in animal studies. Individuals affected in the French case showed neurological signs and symptoms such as headache, photophobia, altered consciousness, and convulsions. These appeared about 4 days after intoxication and, in individuals who recovered, recurrent headaches and weakness persisted for at least 4 years. Studies in animals have confirmed the reversibility of the effects. Trimethyltin produces neuronal necrosis, particularly in the hippocampus and other structures in the limbic system, and this has been demonstrated in humans and in animals. Studies in animals have described neuronal necrosis in the neocortex, pyriform cortex, hippocampal formation, basal ganglia, brain stem, spinal cord, and dorsal root ganglia. The morphological changes that occur in the brain translate into behavioral alterations, such as aggression (both in humans and in animals), memory loss, and unresponsiveness. Some neurological symptoms can last for years. No population group has been identified that has undergone long-term exposure to low levels of trimethyltin or triethyltin, and no monitoring data are available to evaluate current exposures of the general population, but it is unlikely that adverse neurological effects would occur in humans exposed to environmental levels of organotins.

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**Reproductive/Developmental Effects.** There are no data regarding reproductive/developmental effects of inorganic or organic tin compounds in humans. Much of the information available in animals comes from studies conducted in the 1990s. Numerous studies have been conducted with tributyltin, triphenyltin, and dibutyltin which have been shown to cause pregnancy failure, preimplantation loss, postimplantation loss, resorptions, and fetal death. The highest incidence of resorptions and postimplantation losses occurred when the chemicals were administered on gestation days 7–9. Organotins have also proved to be embryotoxic and teratogenic in the same studies cited above and in additional studies. The most commonly seen malformation was cleft palate and other facial malformations. For dibutyltin dichloride, the highest incidence of malformations occurred when dosing on gestation day 8. A key issue in evaluating reproductive/developmental effects has been to ascertain whether the effects occur secondary to maternal toxicity or occur in the absence of maternal toxicity. Thus far, a conclusive answer has not been provided. Two multigeneration studies in rats with tributyltin chloride showed slight alterations in developmental landmarks in male and female animals suggesting a possible endocrine modulatory role for this compound in laboratory rats. However, further studies are necessary to establish the relevancy of these findings to human exposures.

**Hematological Effects.** No data were located regarding hematological effects of inorganic tin or organotins in humans. Tin affects the metabolism of a number of essential minerals such as iron, copper, zinc, calcium, and selenium by mechanisms that are not totally clear, but which could involve altered absorption and/or retention. Studies in animals have shown that excess dietary tin reduces serum iron and copper levels. Thus, as expected, feeding a diet with excess tin to rats produced signs of anemia, which was reversed by enriching the diet with iron and/or copper. A 13-week dietary study of rats fed various levels of stannous chloride was used to derive an intermediate-duration oral MRL for inorganic tin. The MRL is several times higher than the estimates of daily intake of tin from the diet in the U.S. general population. However, it is reasonable to assume that individuals with low levels of iron or copper may be at risk of developing signs of anemia if at the same time they consume excessive amounts of tin.

Organotin compounds have produced hematological effects in laboratory animals. In a 13-week study with dibutyltin dichloride in rats, the most sensitive end point was hemoglobin concentration which was depressed at a dose of 5.7 mg/kg/day, but not at 3.4 mg/kg/day. Long-term studies with tributyltin oxide in rats also have produced decreased hemoglobin concentrations. Since there was an indication of increased young erythrocytes and decreased serum iron concentrations, it was suggested that exposure to tributyltin oxide disrupts hemoglobin synthesis by interfering with iron uptake or by promoting iron loss. Exposure of rats to dioctyltin dichloride also reduced hemoglobin concentration in rats in a 6-week

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dietary study. Whether signs of anemia occur in humans exposed to environmental levels of organotin compounds is not known and, although plausible, this seems unlikely.

### 2.3 MINIMAL RISK LEVELS (MRLs)

#### *Inhalation MRLs*

No inhalation MRLs were derived for inorganic tin or organic tin compounds since adequate experimental data were not available by this route of exposure.

#### *Oral MRLs*

***Inorganic Tin.*** No acute-duration oral MRL was derived for inorganic tin due to insufficient data. Acute data were limited to the NTP (1982) study in which rats and mice were given either a single dose of stannous chloride or were treated for 14 days. These pilot studies of limited scope were designed to establish dose levels to be tested in longer-term studies. The intermediate-duration database is based on a limited number of studies, but a 13-week study in rats provided sufficient information for derivation of an intermediate oral MRL for tin. No chronic-duration MRL was derived for inorganic tin because the lowest dose tested, 0.7 mg Sn/kg/day as stannous chloride, reduced survival in rats in a 42-month drinking water study (Schroeder et al. 1968).

- An MRL of 0.3 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to inorganic tin.

The intermediate-duration MRL was based on a no-observed-adverse-effect level (NOAEL) of 32 mg Sn/kg/day (as stannous chloride) for hematological effects in Wistar rats fed the test material in the diet for 13 weeks (De Groot et al. 1973). The dietary levels tested were 0, 9.5, 32, 95, and 315 mg/kg/day. End points monitored included survival, body weight, food intake, hematology (hemoglobin, hematocrit, total erythrocytes, total and differential leukocytes), serum chemistry (transaminases, alkaline phosphatase, bilirubin), urinalysis, organ weights (nine organs), and gross and microscopic pathology. Tin in the standard diet was not determined, but the concentrations of calcium, phosphorus, iron, copper, and zinc were known. The highest dietary level tested caused reduced food consumption and abdominal distension on week 1. At week 8, loss of body weight occurred in males and females and one male died. At week 9, another three males died and the group was discontinued. Rats in the 95 mg/kg/day group showed poor appetite and abdominal distension the first 2 weeks; this was associated with decreased food consumption, but they continued growing. At termination, no significant differences in body weight were seen. Food consumption was also low in the 32 mg/kg/day group but only for week 1. Hemoglobin concentration was significantly reduced starting at week 4 in the 95 and 315 mg/kg/day groups (about

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12 and 20%, respectively), and at week 4 in the 32 mg/kg/day males (3% reduction). Terminal hemoglobin and hematocrit were significantly reduced only in high-dose treated males (6 and 4%, respectively). Tin had no noticeable effect on osmotic resistance of the erythrocytes or on the number of reticulocytes. Serum alkaline phosphatase was significantly decreased at termination in both sexes, but there was no significant effect on transaminases or in bilirubin concentration. Terminal urine samples were unremarkable, as were relative organ weights. Rats from the high-dose group (315 mg/kg/day) that had to be terminated early showed distended intestines, slight edema of the pancreas, and grayish-brown livers. The high-dose rats had moderate testicular degeneration, severe pancreatic atrophy, spongy white matter in the brain, acute bronchopneumonia, enteritis, and liver changes characterized by homogeneous appearance of the liver cell cytoplasm and mild proliferation of the bile duct epithelium. In the 95 mg/kg/day group, treatment-related effects included bile duct epithelium proliferation and homogeneous cytoplasm at termination. Applying an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to the NOAEL of 32 mg/kg/day yields an intermediate-duration MRL of 0.3 mg/kg/day for inorganic tin. The 95 mg/kg/day dose level is considered a minimal LOAEL based on the unknown biological significance of a 12% reduction in hemoglobin concentration.

Derivation of oral MRLs was considered for the following organotin compounds: tributyltin, triethyltin, trimethyltin, triphenyltin, dibutyltin, and dioctyltin. These are the organotins that have been subject to the most studies. Of these, relevant and adequate information was found only for tributyltin, for which an intermediate-duration MRL and a chronic-duration MRL were derived, and for dibutyltin, for which an intermediate-duration oral MRL was derived.

***Dibutyltin.*** One of the lowest-observed-adverse-effect levels (LOAELs) for acute oral exposure to dibutyltin was 3.8 mg/kg/day for a reproductive effect in rats, a significant increase in postimplantation loss per litter, a serious LOAEL (Ema and Harazono 2000). The highest NOAEL below that LOAEL was 2.5 mg/kg/day for developmental effects in rats (Ema et al. 1991b), which is very near the serious LOAEL. The chronic-duration database was limited to the NCI (1978a) study in which a relatively low dose, 6.7 mg/kg/day caused significant early mortality in rats. An intermediate-duration oral MRL was derived for dibutyltin dichloride.

- An MRL of 0.005 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to dibutyltin dichloride.

The intermediate-duration oral MRL of 0.005 mg/kg/day for dibutyltin dichloride is based on a LOAEL of 5 mg/kg/day for immunological effects in rats (Seinen et al. 1977b). Groups of male weanling Wistar rats were fed diets containing 0, 50, or 150 ppm of the test material (>98% pure) for 4–6 weeks. Based



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on a body weight of 0.2 kg, it can be estimated that these levels provided doses of dibutyltin dichloride of approximately 0, 5, and 15 mg/kg/day (EPA 1988e). End points examined included body weight and parameters of humoral and cellular immune responses. The humoral immune response was assessed by measuring antibody formation against SRBC and *E. coli* lipopolysaccharide. The cellular humoral response was assessed by examining allograft rejection. Final body weight after 4 weeks of exposure was not significantly altered relative to controls, but it was 28% lower than controls in the high-dose group after 6 weeks of exposure. Allograft rejection time was significantly delayed in the high-dose group relative to controls. In the tests for humoral response, the number of antibody-producing cells per million spleen cells was not affected, but the number per whole spleen was significantly decreased in a dose-related manner. This response was associated with a decreased hemagglutination titer in the high-dose group. The antibody titers against *E. coli* lipopolysaccharide were slightly but not significantly lower in treated groups than in controls. The dose of 5 mg/kg/day is the study LOAEL based on the reduction in hemagglutinating antibodies against SRBC. Applying an uncertainty factor of 1,000 (10 for animal to human extrapolation, 10 for use of a LOAEL, and 10 for species variability) to the LOAEL of 5 mg/kg/day yields an intermediate-duration oral MRL of 0.005 mg/kg/day for dibutyltin dichloride.

***Diocetyl***. Only one acute-duration study was available that provided limited information on systemic effects and on effects on the immune system (Seinen et al. 1977a). Intermediate-duration studies focused mainly on the immune system and a relatively low dose tested, approximately 7 mg/kg/day, caused significantly mortality in guinea pigs after 4–5 weeks of treatment (Seinen et al. 1977b). No chronic-duration studies were located.

***Triphenyl***. Most acute-duration studies provide information on reproductive and developmental effects and NOAELs and LOAELs are around 3–6 mg/kg/day. A dose level of 4.7 mg/kg/day was a serious reproductive LOAEL in rats (Ema et al. 1997b). An intermediate-duration study reported high lethality (100%) in rats at approximately 23 mg/kg/day, but did not report whether deaths occurred at lower dose levels tested (NCI 1978b). That study also reported that the lowest dose tested, approximately 5 mg/kg/day, caused 25% reduction in body weight gain, a serious effect. An intermediate-duration study in dogs was not available for review. High lethality was observed in rats in a chronic-duration study with the lowest dose level tested, 0.4 mg/kg/day (Tennekes et al. 1989b).

***Triethyl***. Most dose levels of triethyltin caused serious effects (primarily neurological) both in acute and intermediate duration oral studies. The highest NOAEL in an acute study was 2 mg/kg/day for neurological effects in a study by Snoeij et al. (1985), but that same dose level was a serious LOAEL for body weight in rats in that same study and caused ataxia and paralysis in a different study (Magee et al.

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1957). The highest intermediate LOAEL was 0.66 mg/kg/day for body weight in rats (Purves et al. 1991), but 1.4 mg/kg/day was lethal to rats (Smith 1973) and 0.7–0.8 mg/kg/day were serious neurological LOAELs (Eto et al. 1971; Purves et al. 1991; Reiter et al. 1980). No chronic-duration studies were located.

**Trimethyltin.** Most acute- and intermediate-duration studies of trimethyltin described serious neurological effects occurring at the lowest dose levels tested. The highest acute-duration NOAEL was 0.7 mg/kg/day for neurological effects in rats (Snoeijs et al. 1985), but 1 mg/kg/day was a serious neurological LOAEL (self-mutilating and aggressive behavior) in rats (Bouldin et al. 1981). Doses  $\geq 2$  mg/kg/day were lethal (Brown et al. 1984; Nolan et al. 1990; Snoeijs et al. 1985). In the few intermediate-duration studies available, the lowest LOAEL was 0.05 mg/kg/day for impaired performance of rat pups in a learning task, but there was no dose-response relationship (Noland et al. 1982). No chronic-duration studies were located.

**Tributyltin.** The lowest dose tested in acute-duration studies was 1 mg/kg/day and caused hyperactivity and dysfunction of spatial learning performance in adult rats whose mothers were exposed during pregnancy; no other dose levels were tested (Gardlung et al. 1991). This developmental effect is considered serious, which precludes its use for MRL derivation. Another relatively low dose, 2.5 mg/kg/day for 6 days, caused significant weight loss in rats, a serious effect (Yallapragada et al. 1991). Intermediate- and chronic-duration oral MRLs were derived for tributyltin.

- An MRL of 0.0003 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to tributyltin oxide.

The intermediate-duration oral MRL of 0.0003 mg/kg/day for tributyltin oxide is based on a NOAEL of 0.025 mg/kg/day for immunological effects in rats (Vos et al. 1990). Groups of male Wistar rats were fed a diet containing 0, 0.5, 5, or 50 ppm tributyltin oxide (95.3% pure) for 4.5–6 months. This diet provided approximately 0, 0.025, 0.25, and 2.5 mg/kg/day of the test material. Parameters of specific resistance evaluated included immunoglobulin M (IgM) and immunoglobulin G (IgG) response to ovalbumin and delayed-type hypersensitivity (DTH) response to ovalbumin and tuberculin after 6 months of treatment; resistance to *Trichinella spiralis* infection after 5.5 months; mitogenic response of thymus and spleen cells after 4.5 months; and surface marker analysis of mesenteric lymph nodes after 6 months. Parameters of nonspecific resistance examined included clearance of *Listeria monocytogenes* from the spleen after injection at 5 months and natural cell-mediated cytotoxicity of spleen and peritoneal cells after 4.5 months. Neither body weight nor spleen weight were significantly altered after 4.5 months of treatment, but thymus weight was reduced by 17% relative to controls in the high-dose group. Neither the IgM nor IgG response to ovalbumin and *T. spiralis* were altered after 5.5 months of exposure. The

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immunoglobulin E (IgE) responses to *T. spiralis*, as determined by the passive cutaneous anaphylaxis reaction, was suppressed in a dose-related manner (significant in the mid- and high-dose groups). The DTH reactions to ovalbumin and tuberculin were not significantly altered after 6 months of dosing. There was an increase in the number of larvae *T. spiralis* in muscle after infection in the mid- and high-dose groups after 5.5 months of exposure to the test material. No significant effect was observed on the response of spleen cells to T- and B-mitogens after 4.5 months. The cell surface marker analysis of mesenteric lymph node cells showed a reduction in the relative count of T-lymphocytes and an increase in the percentage of B-lymphocytes in the mid- and high-dose groups after 6 months of treatment. The *in vivo* clearance of *L. monocytogenes* was impaired in the high-dose group after 5 months of treatment. Treatment with tributyltin oxide did induce a consistent effect on the natural killer cell activity of spleen and peritoneal cells after 4.5 months of exposure (decreased with low dose, increased with mid dose, and decreased with high dose). Based on the depression of IgE titers and increased *T. spiralis* in muscle after 5.5 months of exposure to tributyltin oxide, the study LOAEL is 0.25 mg/kg/day and the NOAEL is 0.025 mg/kg/day. Applying an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for intraspecies variability) to the NOAEL yields an intermediate-duration oral MRL of 0.0003 mg/kg/day.

- An MRL of 0.0003 mg/kg/day has been derived for chronic-duration oral exposure (365 days or more) to tributyltin oxide.

The chronic-duration oral MRL of 0.0003 mg/kg/day for tributyltin oxide is based on a NOAEL of 0.025 mg/kg/day for immunological effects in rats (Vos et al. 1990). Groups of male Wistar rats were fed a diet containing 0, 0.5, 5, or 50 ppm tributyltin oxide (95.3% pure) for 18 months. This diet provided approximately 0, 0.025, 0.25, and 2.5 mg/kg/day of the test material. Parameters of specific resistance evaluated included IgM and IgG response to sheep red blood cells (SRBC) after 16 months; IgM and IgG response to ovalbumin and DTH response to ovalbumin and tuberculin after 15 months of treatment; resistance to *T. spiralis* infection after 16.5 months; mitogenic response of thymus and spleen cells after 16.5 months; and surface marker analysis of mesenteric lymph nodes after 18 months. Parameters of nonspecific resistance examined included clearance of *L. monocytogenes* from the spleen after injection at 17 months and natural cell-mediated cytotoxicity of spleen and peritoneal cells after 16 months. No information was provided regarding body weight or weight of the thymus and spleen weights at termination. Exposure to tributyltin oxide did not affect the primary IgM nor the secondary response to SRBC after 16 months of dosing. Neither the IgM nor IgG response to ovalbumin and *T. spiralis* were altered after 15 months of exposure, but the IgE responses to *T. spiralis*, as determined by the passive cutaneous anaphylaxis reaction, was suppressed in a dose-related manner (significant in the mid- and high-dose groups). The DTH reactions to ovalbumin and tuberculin were not significantly altered after 16 months of dosing. There was an increase in the number of larvae *T. spiralis* in muscle after infection

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in the mid- and high-dose groups after 16.5 months of exposure to the test material. No significant effect was observed on the response of spleen cells to T- and B-mitogens after 16 months. The cell surface marker analysis of mesenteric lymph node cells showed a reduction in the relative count of T-lymphocytes and an increase in the percentage of B-lymphocytes in the mid- and high-dose groups after 18 months of treatment. The *in vivo* clearance of *L. monocytogenes* was impaired in the high-dose group after 17 months of treatment. Treatment with tributyltin oxide for 16 months significantly reduced the natural killer cell activity of spleen and peritoneal cells, but there was no clear dose-response relationship. Based on the depression of IgE titers and increased *T. spiralis* in muscle after 16.5 months of exposure to tributyltin oxide, the study LOAEL is 0.25 mg/kg/day and the NOAEL is 0.025 mg/kg/day. Applying an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for intraspecies variability) to the NOAEL yields a chronic-duration oral MRL of 0.0003 mg/kg/day.